OIPE ON THE TRANSMENT

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nGPCR-60. Table 1 below identifies the novel gene sequence nGPCR-x designation, the SEQ ID NO: of the gene sequence, the SEQ ID NO: of the polypeptide encoded thereby, and the U.S. Provisional Application in which the gene sequence has been disclosed.

Table 1

uGPCR	Nucleotide Sequence (SEQ ID NO:)	Amino acid Sequence (SEQ ID NO:)	Originally filed in:		nGPCR	Nucleotide Sequence (SEQ ID NO:)	Amino acid Sequence (SEQ ID NO:)	Originally filed in:
				<u>L</u>				
1	1	2	A	L.	32	39	40	В
1	73	74	Е	L_	33	41	42	С
3	3	4	A	_	34	43	44	C
3	185	186	P	L.	35	45	46	С
4	5	6	Α		36	47	48	С
5	7	8	Α		37	49	50	С
5	75	76	F		38	51	52	C
9	9	10	A		- 40	53	54	С
9	77	78	G		40	83	84	J
11	11	12	Α		41	55	56	С
11	79	80	Н		53	57	58	D
12	13	14	Α		54	59	60	D
14	15	16	A	Г	54	85	86	K
15	17	18	Α		55	61	62	D
18	19	20	Α		56	63	64	D
16	21	22	В		56	87	88	L
16	81	82	1		56	89	90	M
17	23	24	В		57	65	66	D
20	25	26	В		58	67	68	D
21	27	28	В		58	91	92	N
22	29	30	В		58	93	94	0
24	31	32	В		59	69	70	D
27	33	34	В		60	71	72	D
28	35	36	В					
31	37	38	В					

Legend

	A= Ser. No. 60/165,838	I= Ser. No. 60/186,530
	B= Ser. No. 60/166,071	J= Ser. No. 60/207,094
10	C= Ser. No. 60/166,678	K= Ser. No. 60/203,111
	D= Ser. No. 60/173,396	L= Ser. No. 60/190,310
	E= Ser. No. 60/184,129	M= Ser. No. 60/201,190
	F= Ser. No. 60/188,114	N= Ser. No. 60/185554
	G= Ser. No. 60/185,421	O= Ser. No. 60/190,800
15	H= Ser. No. 60/186,811	P= Ser. No. 60/198,568

When a specific nGPCR is identified (for example nGPCR-5), it is understood that only that specific nGPCR is being referred to.

As described in Example 4 below, the genes encoding nGPCR-1 (nucleic acid sequence SEQ ID NO: 1, SEQ ID NO: 73, amino acid sequence SEQ ID NO: 2, SEQ ID NO:74), nGPCR-9 (nucleic acid sequence SEQ ID NO:9, SEQ ID NO:77, amino acid sequence SEQ ID NO:10, SEQ ID NO:78), nGPCR-11 (nucleic acid sequence

SEQ ID NO:11, SEQ ID NO:79, amino acid sequence SEQ ID NO:12, SEQ ID NO:80), nGPCR-16 (nucleic acid sequence SEQ ID NO: 21, SEQ ID NO:81, amino acid sequence SEQ ID NO: 22, SEQ ID NO:82), nGPCR-40 (nucleic acid sequence SEQ ID NO:53, SEQ ID NO:83, amino acid sequence SEQ ID NO:54, SEQ ID NO:84), nGPCR-54 (nucleic acid sequence SEQ ID NO:59, SEQ ID NO:85, amino acid sequence SEQ ID NO:60, SEQ ID NO: 86), nGPCR-56 (nucleic acid sequence SEQ ID NO:63, SEQ ID NO:87, SEQ ID NO:89, amino acid sequence SEQ ID NO:64, SEQ ID NO: 88, SEQ ID NO:90), nGPCR-58 (nucleic acid sequence SEQ ID NO:67, SEQ ID NO:91, SEQ ID NO:93, amino acid sequence SEQ ID NO:68, SEQ ID NO:92, SEQ ID NO:94) and nGPCR-3 (nucleic acid sequence SEQ ID NO:3, SEQ ID NO:185, amino acid sequence SEQ ID NO:4, SEQ ID NO: 186) have been detected in brain tissue indicating that these n-GPCR-x proteins are neuroreceptors.

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The invention provides purified and isolated polynucleotides (e.g., cDNA, genomic DNA, synthetic DNA, RNA, or combinations thereof, whether single- or double-stranded) that comprise a nucleotide sequence encoding the amino acid sequence of the polypeptides of the invention. Such polynucleotides are useful for recombinantly expressing the receptor and also for detecting expression of the receptor in cells (e.g., using Northern hybridization and in situ hybridization assays). Such polynucleotides also are useful in the design of antisense and other molecules for the suppression of the expression of nGPCR-x in a cultured cell, a tissue, or an animal; for therapeutic purposes; or to provide a model for diseases or conditions characterized by aberrant nGPCR-x expression. Specifically excluded from the definition of polynucleotides of the invention are entire isolated, non-recombinant native chromosomes of host cells. A preferred polynucleotide has the sequence of the sequence set forth in odd numbered sequences ranging from SEQ ID NO: 1 to SEQ ID NO: 93 and SEQ ID NO: 185, which correspond to naturally occurring nGPCR-x sequences. It will be appreciated that numerous other polynucleotide sequences exist that also encode nGPCR-x having the sequence set forth in even numbered sequences ranging from SEQ ID NO: 2 to SEQ ID NO: 94 and SEQ ID NO: 186, due to the well-known degeneracy of the universal genetic code.

The invention also provides a purified and isolated polynucleotide comprising a nucleotide sequence that encodes a mammalian polypeptide, wherein the polynucleotide hybridizes to a polynucleotide having the sequence set forth in odd numbered sequences ranging from SEQ ID NO: 1 to SEQ ID NO: 93 and SEQ ID

774; Ubl & Reiser. (1997) Glia 21:361-369; Grabham & Cunningham (1995) J Neurochem 64:583-591.

nGPCR-x receptor activation may mediate neuronal and astrocyte apoptosis and prevention of neurite outgrowth. Inhibition would be beneficial in both chronic and acute brain injury. See, e.g., Donovan et al. (1997) J Neurosci 17:5316-5326; Turgeon et al (1998) J Neurosci 18:6882-6891; Smith-Swintosky et al. (1997) J Neurochem 69:1890-1896; Gill et al. (1998) Brain Res 797:321-327; Suidan et al. (1996) Semin Thromb Hemost 22:125-133.

The attached Sequence Listing contains the sequences of the polynucleotides and polypeptides of the invention and is incorporated herein by reference in its entirety.

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As described above and in Example 4 below, the genes encoding nGPCR-1 (nucleic acid sequence SEQ ID NO: 1, SEQ ID NO: 73, amino acid sequence SEQ ID NO: 2, SEQ ID NO:74), nGPCR-9 (nucleic acid sequence SEQ ID NO:9, SEQ ID NO:77, amino acid sequence SEQ ID NO:10, SEQ ID NO:78), nGPCR-11 (nucleic acid sequence SEQ ID NO:11, SEQ ID NO:79, amino acid sequence SEQ ID NO:12, SEQ ID NO:80), nGPCR-16 (nucleic acid sequence SEQ ID NO: 21, SEQ ID NO:81, amino acid sequence SEQ ID NO: 22, SEQ ID NO:82), nGPCR-40 (nucleic acid sequence SEQ ID NO:53, SEQ ID NO:83, amino acid sequence SEQ ID NO:54, SEQ ID NO:84), nGPCR-54 (nucleic acid sequence SEQ ID NO:59, SEQ ID NO:85, amino acid sequence SEQ ID NO:60, SEQ ID NO: 86), nGPCR-56 (nucleic acid sequence SEQ ID NO:63, SEQ ID NO:87, SEQ ID NO:89, amino acid sequence SEQ ID NO:64, SEQ ID NO: 88, SEQ ID NO:90), nGPCR-58 (nucleic acid sequence SEQ ID NO:3, SEQ ID NO:185, amino acid sequence SEQ ID NO:4, SEQ ID NO: 186) have been detected in brain tissue indicating that these n-GPCR-x proteins are neuroreceptors. The identification of modulators such as agonists and antagonists is therefore useful for the identification of compounds useful to treat neurological diseases and disorders. Such neurological diseases and disorders, including but are not limited to, schizophrenia, affective disorders, ADHD/ADD (i.e., Attention Deficit-Hyperactivity Disorder/Attention Deficit Disorder), and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, and senile dementia as well as depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like.

ACTCCTCGGTGCTGTTCAGGTGTTTCTGGAATGGATCTTCTAGTTTCTGCTGGTAGATCCAGGAAGCATTCTGAAGTTTTTCCATCCCTGA

The following amino acid sequence <SEQ ID NO. 18> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 17:

SGMEKLQNASWIYQQKLEDPFQKHLNSTEEYLAFLCGPRRSHFFLPVSVVYVPIFVVGVIGNVLVCLVILQHQ AMKTPNTYYLFSLAVSDLLVLLLGMPLEVYEMWRNYPFLFGPVGCYFKTALFETVCFASILSITTVSVERYVA ILHPFRAKLQSTRRRALRILGIVWGFSVLFSLPNTSIHGIKFHYFPNGSLVPGSATCTVIKPMWIYNFIIQVT SFLFYLLPMTVISVLYYLMALRVSIAGVAG

The following DNA sequence beGPCR-seq18 <SEQ ID NO. 19> was identified in H. sapiens:

The following amino acid sequence <SEQ ID NO. 20> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 19:

IKMIFAIVQIIGFSNSICNPIVYAFMNENFKKNVLSAVCYCIVNKTFSPAQRHGNSGITMMRKKAKFSLRENP

The following DNA sequence beGPCR-seq16 <SEQ ID NO. 21> was identified in H. sapiens:

The following amino acid sequence <SEQ ID NO. 22> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 21:

VSYSGAFSPPGDFPSMPGHNTSRNSSCDPIVTPHLISLYFIVLIGGLVGVISILFLLVKMNTRSVTTMAVINL VVVHSVFLLTVPFRLTYLIKKTWMFGLPFCKFVSAMLHIHMYLTVPILCGDPGHQIPHLLQVQRQSGILQKTA

The following DNA sequence beGPCR-seq17<SEQ ID NO. 23> was identified in H. sapiens:

The following amino acid sequence <SEQ ID NO. 24> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 23:

 ${\tt CEYLFESWGI} \underline{RLAVWAIVLLSVLCNGLVLLTVFAG} {\tt GPAPLPPVKFVVGAIAGANTLT} \underline{GISCGLLASVDALTLV} {\tt S}$

The following DNA sequence beGPCR-seq20 <SEQ ID NO. 25> was identified in H. sapiens:

The following amino acid sequence <SEQ ID NO. 78> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 77:

MESGLLRPAPVSEVIVLHYNYTGKLRGARYQPGAGLRADAVVCLAVCAFIVLENLAVLLVLGRHPRFHAPMFL LLGSLTLSDLLAGAAYAANILLSGPLTLKLSPALWFAREGGVFVALTASVLSLLAIALERSLTMARRGPAPVS SRGRTLAMAAAAWGVSLLLGLLPALGWNCLGRLDACSTVLPLYAKAYVLFCVLAFVGILAAICALYARIYCQV RANARRLPARPGTAGTTSTRARRKPRSLALLRTLSVVLLAFVACWGPLFLLLLLDVACPARTCPVLLQADPFL GLAMANSLLNPIIYTLTNRDLRHALLRLVCCGRHSCGRDPSGSQQSASAAEASGGLRRCLPPGLDGSFSGSER SSPQRDGLDTSGSTGSPGAPTAARTLVSEPAAD

The following DNA sequence nGPCR-11 <SEQ ID NO. 79> was identified in H. sapiens:

The following amino acid sequence <SEQ ID NO. 80> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 79:

MYMGSCCRIEGDTISQVMPPLLIVAFVLGALGNGVALCGFCFHMKTWKPSTVYLFNLAVADFLLMICLPFRTD
YYLRRRHWAFGDIPCRVGLFTLAMNRAGSIVFLTVVAADRYFKVVHPHHAVNTISTRVAAGIVCTLWALVILG
TVYLLLENHLCVQETAVSCESFIMESANGWHDIMFQLEFFMPLGIILFCSFKIVWSLRRRQQLARQARMKKAT
RFIMVVAIVFITCYLPSVSARLYFLWTVPSSACDPSVHGALHITLSFTYMNSMLDPLVYYFSSPSFPKFYNKL
KICSLKPKQPGHSKTQRPEEMPISNLGRRSCISVANSFQSQSDGQWDPHIVEWH

The following DNA sequence nGPCR-16 <SEQ ID NO. 81> was identified in H. sapiens:

anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-x modulators, including nGPCR-x ligands and anti-nGPCR-x antibodies, to treat individuals having such disease states is intended as an aspect of the invention.

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EXAMPLE 4: TISSUE EXPRESSION PROFILING

Tissue specific expression of the cDNAs encoding nGPCR-1, nGPCR-3, nGPCR-9, nGPCR-11, nGPCR-16, nGPCR-40, nGPCR-54, nGPCR-56, and nGPCR-58 was detected using a PCR-based system. Tissue specific expression of cDNAs encoding nGPCR-x may be accomplished using similar methods.

Primers were synthesized by Genosys Corp., The Woodlands, TX. PCR reactions were assembled using the components of the Expand Hi-Fi PCR SystemTM (Roche Molecular Biochemicals, Indianapolis, IN).

nGPCR-1

The RapidScanTM Gene Expression Panel was used to generate a comprehensive expression profile of the putative GPCR in human tissues. Human tissues in the array may include: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, fetal liver. Human brain regions in the array may include: frontal lobe, temporal lobe, cerebellum, hippocampus, substantia nigra, caudate nucleus, amygdala, thalamus, hypothalamus, pons, medulla and spinal cord.

Expression of the nGPCR-1 in the various tissues was detected by using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a 212bp fragment in the presence of the appropriate cDNA. The forward primer was:

GCTCAACCCACTCATCTATGCC (SEQ ID NO: 97), and the reverse primer was:

AAACTTCTCTGCCCTTACCGTC (SEQ ID NO: 98)

The PCR reaction mixture was added to each well of the PCR plate. The plate was placed in a GeneAmp PCR9700 PCR thermocycler (Perkin Elmer Applied Biosystems). The plate was then exposed to the following cycling parameters: Presoak 94°C for 3 min; denaturation at 94°C for 30 seconds; annealing at primer T_m for

disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-11 modulators, including nGPCR-11 ligands and anti-nGPCR-11 antibodies, to treat individuals having such disease states is intended as an aspect of the invention.

Expression of nGPCR-11 in the thyroid gland, indicates that agonists or antagonists could be of use in the treatment of thyroid dysfunction such as thyreotoxicosis and myxoedema. They could also be of use in the stimulation of thyroid hormone release leading to overall increase in metabolic rate and weight reduction. The expression of nGPCR-11 in liver and muscle indicate a use for agonists or antagonists in regulation of glucose metabolism applicable in diabetes type II.

nGCPR-16

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The RapidScanTM Gene Expression Panel was used to generate a comprehensive expression profile of the putative GPCR in human tissues. Human tissues in the array included, *inter alia*: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, fetal liver. Human brain regions in the array included, *inter alia*: frontal lobe, temporal lobe, cerebellum, hippocampus, substantia nigra, caudate nucleus, amygdala, thalamus, hypothalamus, pons, medulla and spinal cord.

Expression of nGPCR-16 in the various tissues was detected by using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a 205bp fragment in the presence of the appropriate cDNA. The forward primer used to detect expression of nGPCR-16 was:

5' CAGCCCAAACATCCAAGTC 3'. (SEQ ID NO: 113). The reverse primer used to detect expression of nGPCR-16 was:

5' ACCCCACTTAATCAGCCTC 3'(SEQ ID NO: 114).

For detection of expression within brain regions, the same primer set was used with the Human Brain Rapid ScanTM Panel (OriGene Technologies, Rockville, MD). This panel represents serial dilutions over a 2 log range of first strand cDNA from the following brain regions arrayed in a 96 well format: frontal lobe, temporal lobe, cerebellum, hippocampus, substantia nigra, caudate nucleus, amygdala, thalamus, hypothalamus, pons, medulla and spinal cord.

												•			
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Pro I	His	Leu 35	Ile	Ser	Leu	Tyr	Phe 40	Ile	Val	Leu	Ile	Gly 45	Gly	Leu	Val
Gly (Val 50	Ile	Ser	Ile	Leu	Phe 55	Leu	Leu	Val	Lys	Met 60	Asn	Thr	Arg	Ser
Val 5	Thr	Thr	Met	Ala	Val 70	Ile	Asn	Leu	Val	Val 75	Val	His	Ser	Val	Phe 80
Leu 1	Leu	Thr	Val	Pro 85	Phe	Arg	Leu	Thr	Tyr 90	Leu	Ile	Lys	Lys	Thr 95	Trp
Met 1	Phe	Gly	Leu 100	Pro	Phe	Cys	Lys	Phe 105	Val	Ser	Ala	Met	Leu 110	His	Ile
His N	Met	Tyr 115	Leu	Thr	Val	Pro	Ile 120	Leu	Суѕ	Gly	Asp	Pro 125	Gly	His	Gln
Ile I	Pro 130	His	Leu	Leu	Gln	Val 135	Gln	Arg	Gln	Ser	Gly 140	Ile	Leu	Gln	Lys

Thr Ala Cys Cys Gly

<210> 23 <211> 222

Page 15

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- Met Asn Arg Ala Gly Ser Ile Val Phe Leu Thr Val Val Ala Ala Asp 100 105 110
- Arg Tyr Phe Lys Val Val His Pro His His Ala Val Asn Thr Ile Ser 115 120 125
- Thr Arg Val Ala Ala Gly Ile Val Cys Thr Leu Trp Ala Leu Val Ile 130 135 140
- Leu Gly Thr Val Tyr Leu Leu Leu Glu Asn His Leu Cys Val Gln Glu 150 150 155 160
- Thr Ala Val Ser Cys Glu Ser Phe Ile Met Glu Ser Ala Asn Gly Trp 165 170 175
- His Asp Ile Met Phe Gln Leu Glu Phe Phe Met Pro Leu Gly Ile Ile 180 185 190
- Leu Phe Cys Ser Phe Lys Ile Val Trp Ser Leu Arg Arg Arg Gln Gln
 195 200 205
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Page 54